Trends in Endocrinology & Metabolism

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Review

Emerging Role of Sensory Perception in Aging and Metabolism

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Sensory perception comprises gustatory (taste) and olfactory (smell) modalities as well as somatosensory (pain, heat, and tactile mechanosensory) inputs, which are detected by a multitude of sensory receptors. These sensory receptors are contained in specialized ciliated neurons where they detect changes in environmental conditions and participate in behavioral decisions ranging from food choice to avoiding harmful conditions, thus insuring basic survival in metazoans. Recent genetic studies, however, indicate that sensory perception plays additional physiological functions, notably influencing energy homeostatic processes and longevity through neuronal circuits originating from sensory tissues. Here we review how these findings are redefining metabolic signaling and establish a prominent role of sensory neuroendocrine processes in controlling health span and lifespan, with a goal of translating this knowledge towards managing age-associated diseases.

Trends

The fine-tuning of smell (olfactory) and taste (gustatory) sensitivities is tightly regulated by endocrine signals involved in energy balance, due to the presence of many endocrine receptors on these neurons.

Not much is known about the effect of upstream sensory inputs in the hypothalamus on regulatory mechanisms governing whole-body energy homeostasis. In addition to the obvious role of olfaction and taste in influencing behavioral decisions about food choice, recent studies suggest that olfactory stimuli may contribute to the regulation of energy homeostasis.

Neuroendocrine processes, engaged by sensory afferent neurons expressing transient receptor potential vanilloid 1 (TRPV1), are tightly involved in the maintenance of metabolic homeostasis and play a role in regulating longevity.

Sensory Cues and Hypothalamic Hunger Circuits

The regulation of whole-body energy homeostasis relies on a tight balance between food intake and energy expenditure. To adapt quickly to variations in environmental conditions and maintain global body energy homeostasis, mammalian systems have developed a neurocircuitry within the hypothalamus that integrates external signals into an autonomic response via the sympathetic nervous system. The melanocortin system, namely melanocortin 3 and 4 receptors (MC3R and MC4R), in the arcuate nucleus (ARC) controls feeding in response to circulating insulin ghrelin and leptin levels and relays information to pre-autonomic neurons in the paraventricular nucleus (PVN). In particular, ARC neurons coexpressing the orexigenic neuropeptides agouti-related proteins (AgRPs) (inverse agonists of MC3R and MC4R) and neuropeptide Y (NPY) (agonist of NPY receptor) along with neurons coexpressing anorexigenic pro-opiomelanocortin (POMC) precursor, a precursor of α-MSH that activates MC4R, and cocaine- and amphetamine-related transcript (CART), have been identified as key players in controlling energy balance [1–6]. The ARC and PVN circuits also communicate with the lateral parabrachial nucleus (PBN), which sends anorexigenic projections to the central amygdala (CeA) [7]. The CeA, located in the forebrain region, integrates homeostatic and motivational aspects of feeding in addition to receiving taste sensory input from the brainstem [8]. Bilateral lesion of the CeA induces hyperphagia and obesity in rats [9] and is required for hedonic perception of food as demonstrated in conditioned taste aversion assays [10]. Yamamoto *et al.* demonstrated that both the CeA and the basolateral amygdala (BLA) are required for this behavioral change, which associates the ingestion of a pleasant food to a malaise and promotes enhanced taste sensitivity towards the conditioned stimulus. Inhibitory synaptic inputs from the BLA preferentially innervate and suppress the activity of lateral hypothalamus (LH) glutamatergic neurons to control food intake [11]. The amygdala also communicates taste information to the reward centers of the

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mesolimbic dopaminergic system center, comprising the ventral tegmental area (VTA), the nucleus accumbens (NAc), the medial prefrontal cortex (mPFC), and the orbitofrontal cortex (OFC), which is essential for motivated feeding behaviors with palatable food (Figure 1).

Interestingly, recent technological advances have allowed the natural recording of orexigenic AgRP and anorexigenic POMC neuron activity in awake, behaving animals using an optical method called fiber photometry [12]. The presence of food, without its ingestion, is sufficient to rapidly switch the activation state of these neurons on hunger and can be immediately reversed by removing the food cues. The intensity of the response depends on the palatability of the food presented, revealing that the ARC can rapidly associate food hedonic or energetic value to sensory stimuli and obtain real-time information about food availability and palatability in addition to endocrine signals regulating the nutritional state of the animal. What is the reason for this rapid sensory regulation? It is possible that this mechanism allows an immediate means to inhibit food scavenging or other appetitive behaviors once food has been encountered. More work is required to understand the neuronal circuitry for transmission of these sensory inputs to the ARC.

Olfaction and Energy Balance

Olfactory stimuli are absorbed by the mucosal surfaces lining the main olfactory epithelium (MOE) and septal organ present in many nonhuman mammals [13]. Each molecule is detected

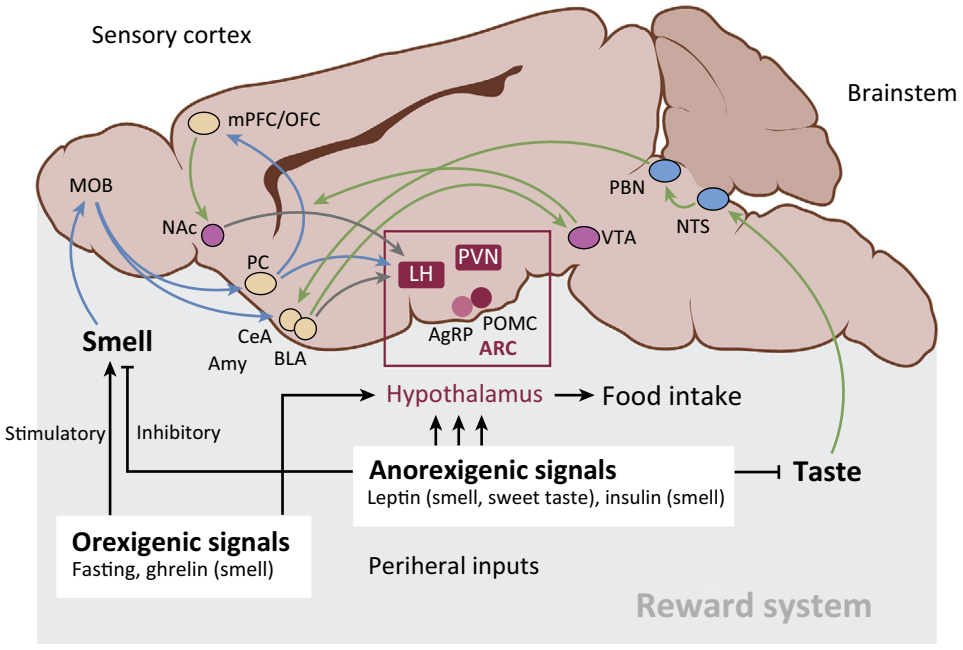

Figure 1. Integrated Model of the Sensory Inputs in the Central Nervous System Regulating Homeostatic and Hedonic Feeding. Taste signals (green) are transmitted via cranial nerves to the nucleus of the tractus solitarius (NTS) and the parabrachial nucleus of the pons (PBN) and further transmitted to the amygdala (Amy) and the cortex. These centers activate the mesolimbic dopamine system, an essential interface between palatability and eating behavior that comprises the ventral tegmental area (VTA) of the midbrain (the major source of dopamine), the nucleus accumbens (NAc), the medial prefrontal cortex (mPFC), and the orbitofrontal cortex (OFC). This system integrates external stimuli through the mPFC and OFC and stimulates the lateral hypothalamus (LH). Olfactory signals (blue) arise from the main olfactory bulb (MOB) and are integrated by the piriform cortex (PC) and the cortical Amy, which transmit the olfactory information to the OFC and the LH. In the hypothalamus, LH GABAergic inputs promote food intake by stimulating the paraventricular nucleus (PVN). Sensory inputs also induce arcuate nucleus (ARC) neuron activity through rapid of orexigenic agouti-related protein (AgRP) neurons and activation of neurons coexpressing anorexigenic pro-opiomelanocortin (POMC), which signal to pre-autonomic neurons of the PVN to initiate a satiety response.

by a specific combination of olfactory sensory neurons (OSNs) expressing a single type of olfactory receptor. All OSNs expressing the same receptor send convergent projections to a few discrete glomeruli in the main olfactory bulb (MOB); each glomerulus integrates afferent signals from thousands of OSNs and relays output via several dozen mitral/tufted cells. Mitral/tufted projections are distributed via the lateral olfactory tract to a heterogeneous assemblage of secondary structures collectively labeled as the olfactory cortex. The piriform cortex (PC) and the cortical amygdala (Amy) are the main recipients of inputs from the MOB and transmit olfactory information to the OFC, the insular cortex, and the LH (Figure 1).

An increasing literature links olfactory acuity to the regulation of energy homeostasis in addition to playing a role in food appreciation and perception. In mice, olfactory sensitivity appears to be dynamically regulated by nutritional status. Before a meal, hunger arouses olfactory perception, facilitating the retrieval and ingestion of food [14–16]. Mechanistically, this enhanced olfactory acuity is mediated by endocannabinoid signaling in the MOB [17]. Fasting induces an increase in endocannabinoid levels in the MOB, resulting in the activation of cannabinoid 1 (CB1) receptors on olfactory cortex axon terminals and consequently reducing the glutamatergic excitation of inhibitory granular cells in the MOB, leading to an increase in odor perception and food intake once the animals are re-exposed to food.

Conversely, a reduction of olfactory sensitivity is observed after the ingestion of a meal and may contribute to a satiety response, suggesting that endocrine signals might dynamically regulate olfactory acuity as part of central fasting and feeding circuits. Supporting this idea, physiological evidence that anorexigenic hormones can decrease olfactory acuity has been established. In an *in vitro* intact epithelium preparation of rat OSNs, patch-clamp recordings show that while insulin and leptin enhance the electrical excitability of OSNs in the absence of odorants, they surprisingly reduce the odorant-induced activity [18]. How are these hormones regulating OSN function? Interestingly, the MOE and MOB contain a large amount of anorexigenic receptors, such as the leptin (Ob-R) and insulin (IR) receptors. The Ob-Rs are localized in brain areas related to olfactory signaling such as the nucleus of the lateral olfactory tract [19], the MOB [20], and olfactory processing centers in the cortex. In mice lacking leptin (*ob/ob*) or leptin receptors (*db/db*), the mean time to find food is approximately ten times shorter than wild type and this effect can be abrogated in *ob/ob* mice by daily leptin injections [21]. These data support a role for leptin in the regulation of olfactory-mediated pre-ingestive behavior by controlling olfactory sensitivity through a leptin receptor-based mechanism.

Insulin, a major anorexigenic hormone secreted by pancreatic β cells, promotes energy uptake in peripheral tissues and acts on hypothalamic circuits to induce energy expenditure. Surprisingly, the MOB contains the highest density of IRs [22] and its concentration of insulin reaches levels as high as observed in the hypothalamus, making this region a major site of insulin action in the brain [23]. Additionally, the highest transport rate of insulin across the blood–brain barrier occurs in the MOB [24], where its degradation is also the fastest in the brain. Consistently, olfactory bulbectomy results in increased sensitivity to peripherally administered insulin as well as lower body weight and reduced blood sugar in adult mice [25]. Interestingly, a conflicting report suggests that increasing olfactory sensitivity prevents diet-induced obesity in mice. Gene-targeted deletion of the voltage-gated K^+ channel (Kv) subtype Kv1.3 causes resistance to DIO [26] and additionally enhances olfactory sensitivity [27]. As Kv1.3 is highly expressed throughout the brain and in non-neuronal tissues including liver and skeletal muscle [26], the improved metabolic profile of these mice may also originate from non-olfactory tissues. Further analysis demonstrated that olfactory bulbectomy suppresses the lean phenotype of the Kv1.3 knockout animals [27]. Taken together, these data suggest that both enhancing and repressing olfactory inputs can result in enhanced metabolic health. Similarly, in the nematode *Caenorhabditis elegans* both

olfactory ablation and enhancement can result in increased lifespan, with olfactory ablation extending lifespan most robustly in worms [28–30]. Better resolution of the metabolic consequences of increased and decreased olfactory acuity in rodents is needed using noninvasive, tissue-specific genetic approaches. Surgical removal of the olfactory bulb can lead to phenotypes that are difficult to interpret because of the variability of ablation among individuals and the latency of the healing process after surgery, which can impact body weight and generate opposite phenotypes related to appetitive behaviors such as increased food intake in obesity-prone rats [31] or prolonged loss of appetite and anorexia [32].

Gustatory Neurotransmission and Metabolism

Once food is ingested, it is sensed by taste buds contained in gustatory papillae on the tongue. Gustatory neurotransmission from the oral cavity is processed through the cranial nerves VII, IX, and X to the nucleus of the solitary tract (NTS) in the brainstem, which in turn exchanges information with the forebrain and peripheral tissues (Figure 1).

The perception of certain nutrients such as sugars and fat have strong reward values and drives dopaminergic signaling in the mesolimbic dopaminergic system, thus favoring motivated feeding behavior towards these highly palatable foods. Excessive consumption of these foods has been strongly linked to the obesity pandemic and diabetes in Western societies. What are the physiological mechanisms driving the palatability of energy-rich foods? The discovery of the sweet-taste receptors T1R2/T1R3 has provided important insights into the understanding of gustatory responses to sweets [33]. Interestingly, sweet-taste perception but not sour or bitter tastes can be modulated by leptin [34,35]. Stimulation with leptin increases K^+ outward conductance of taste cells, thus provoking hyperpolarization and reduction of excitability. In accordance with a role for leptin as an off-switch signal in taste cells, mice lacking leptin receptors (db/db) display enhanced neural responses and elevated preferences towards sweet-tasting compounds [34].

Opposing the effects of leptin, endocannabinoids such as *N*-arachidonoylethanolamide (AEA), also known as anandamide, and 2-arachidonoylglycerol (2-AG) enhance sweet-taste responses through CB1R signaling [36]. Reciprocal regulation of sweet sensitivity by leptin and endocannabinoids is possibly a mechanism to modulate food intake and food-seeking behaviors depending on the nutritional status.

Sugar preference and appetite are also powerfully regulated by post-ingestive mechanisms that trigger dopaminergic release in the brain dopamine centers as demonstrated by intragastric infusion of glucose in the stomach, thus bypassing the oral taste system [37]. Mice that lack a critical component in taste transduction, the TRPM5 ion channel, still develop preference for sugars and palatable amino acids in the absence of sweet taste [37]. Remarkably, the post-ingestive preference for sugars is specific to the metabolically active sugars glucose and galactose and cannot be induced by fructose [38]. The liver plays a prominent role in regulating food intake and sugar preference. Injection of glucose into the liver induces c-fos expression in the NAc, triggering dopamine release [39,40]. How could the liver be involved in the control of this post-ingestion system? Recent evidence implicates fibroblast growth factor (FGF) 21, in the reduction of sweet-seeking behavior and meal size [41]. FGF21 is a liver hormone involved in controlling energy metabolism during fasting through the modulation of hepatic fatty acid oxidation and ketogenesis, increasing insulin sensitivity, while blocking somatic growth [42]. FGF21 heterozygous knockout mice exhibit an increased preference for carbohydrates compared with wild-type littermates, whereas genetic or pharmacological elevation of FGF21 levels suppresses the intake of both simple sugars and non-caloric sweeteners but not lipids or protein [41]. High circulating sugar levels trigger FGF21 secretion from the liver, where it signals to the PVN in the hypothalamus to suppress carbohydrate intake [41].

Taste Receptor Cells in the Gut

Exploration of the nutrient-sensing mechanisms in the taste buds of the tongue revealed the surprising presence of chemosensory taste-like cells in the gut [43]. Remarkably, these cells express gustatory signal transduction elements such as G protein-coupled T1R taste receptors and α-gustducin, the α subunit of the G protein coupled to taste receptors required for bitter, sweet, and umami taste transduction.

These taste signaling components have been identified in enteroendocrine L cells where they regulate the secretion of glucagon-like peptide 1 (GLP-1), an incretin that increases insulin secretion in a glucose-dependent manner, in response to glucose and the non-caloric sweetener sucralose [44]. What is the function of these cells? Because of their distribution along the lumen of the intestine, these cells are ideally placed to sense the luminal contents and play a role in the regulation of nutrient transporter expression, nutrient uptake and the secretion of gut hormones and neurotransmitters controlling energy and glucose homeostasis. Therefore, these cells may be at the interface between the gut lumen and the brain to trigger adaptive responses that affect gastrointestinal function, food intake, and glucose metabolism.

What are the ligands for these cells? Plausible candidates targeting these cells may arise from gut microbiota that interact with the host control of food intake [45]. Breton *et al.* showed that regular nutrient uptake stabilizes exponential growth of *Escherichia coli*, with the stationary phase occurring 20 min after nutrient supply accompanied by bacterial proteome changes, therefore suggesting the recruitment of bacterial proteins in modulating host satiety. Intestinal infusions of *E. coli* stationary phase proteins increased plasma levels of the satiety hormone peptide YY (PYY) and their intraperitoneal injection acutely suppressed food intake and activated c-fos in hypothalamic POMC neurons, while their repeated administration reduced meal size. Surprisingly, ClpB, a bacterial protein mimetic of α-MSH, is upregulated in the *E. coli* stationary phase and stimulated the firing rate of hypothalamic POMC neurons. Although MC4R-mediated α-MSH anorexigenic effects occur in the CNS, a recent study shows that activation of MC4R in gut enteroendocrine cells stimulates release of the satietogenic hormones GLP-1 and PYY [46]. Thus, local gut signaling by microbiota-derived α-MSH-like molecules to enteroendocrine cells is possible and could be mediated by gut gustatory cells.

Visceral Sensing by Afferent Sensory Neurons

Sensory innervation of the upper abdominal viscera (such as the stomach, pancreas, and small intestine) arises via the vagus and spinal nerves, with cell bodies in the nodose ganglion (NG) and dorsal root ganglion (DRG), respectively [47] (Figure 2). DRG afferents innervating the pancreas, stomach, duodenum, and jejunum are largely peptidergic, expressing calcitonin gene-related peptide (CGRP), Substance P (SP), and/or transient receptor potential vanilloid 1 (TRPV1). TRPV1, a major receptor in pain signaling, senses noxious thermal and chemical stimuli, responding to capsaicin, the pungent component of chili peppers [48]. Both TRPV1 and consumption of capsaicin have been linked to changes in metabolism [49]. TRPV1 mutation protects against diet-induced obesity in mice exposed to a high-fat diet by increasing the thermogenic capacity of these animals [50] and increases longevity by improving energy expenditure profiles in old age [51]. In accordance with these results, the SNP Val585Ile on the *Trpv1* gene correlates with loss of adiposity in humans [52]. If these data indicate a beneficial role in metabolic health for reduction of TRPV1 activity, conflicting results suggest that activating these receptors can also promote weight loss. Multiple human studies have assessed the actions of dietary capsaicin and other capsinoids on food intake and energy expenditure. In general, capsaicin was found to reduce food intake and increase energy expenditure [53] and reduce adiposity [54]. Interestingly, systemic capsaicin administration induces ablation of TRPV1-positive fibers and prevents age-onset obesity [55], suggesting that sustained activation of TRPV1 leads to its inactivation. However, the actions of capsaicin could also be independent

Key Figure

Model for Sensory Control of Peripheral Tissues

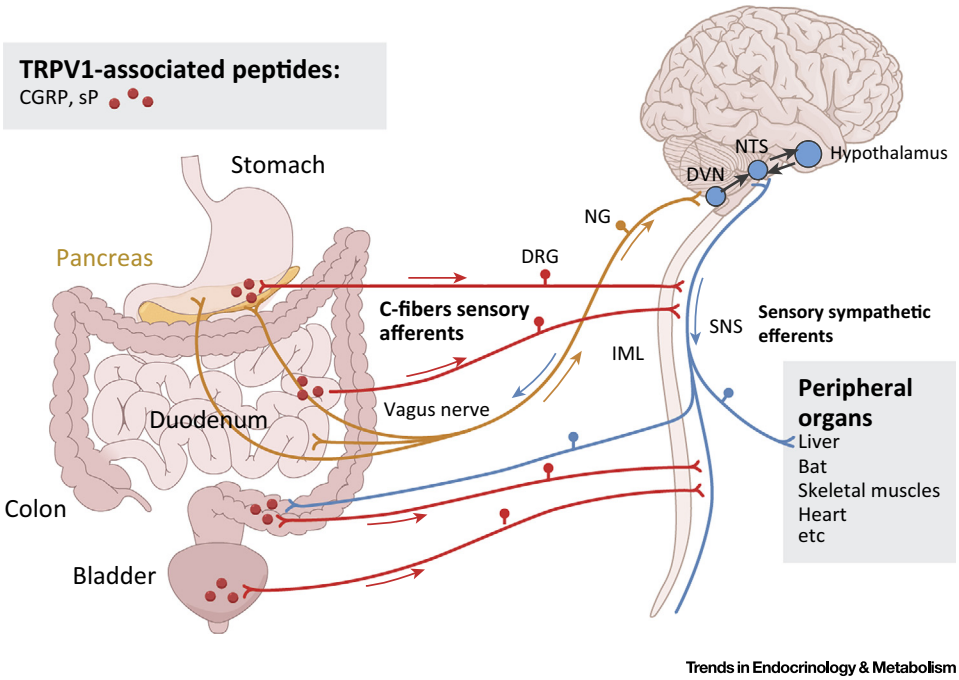

Figure 2. Afferent sensory innervation of upper abdominal viscera (e.g., stomach, pancreas, small intestine) arises via the vagus and spinal nerves, with cell bodies in the nodose ganglion (NG) (orange) and dorsal root ganglion (DRG) (red), respectively. Transient receptor potential vanilloid 1 (TRPV1) is contained in sensory afferent neurons, with the DRG cells being highly peptidergic, expressing calcitonin gene-related peptide (CGRP) and Substance P (SP), whereas very few NG neurons are of peptidergic nature. The vagus nerve transmits afferent input to nucleus of the solitary tract (NTS) neurons (orange arrows), such as sensory signals of gastrointestinal origin. NTS neurons from caudal regions project to vagal efferent neurons in the dorsal motor nucleus vagus (DVN) (blue) to control parasympathetic gastrointestinal responses including insulin secretion and gastric emptying and to the intermediolateral (IML) cell column of the spinal cord along with projections from neurons in other regions of the hindbrain and hypothalamus. These NTS descending inputs (blue arrows) control sympathetic efferent responses through spinal nerves of relevance to energy expenditure and gastrointestinal responses.

of TRPV1 as it can inhibit adipogenesis in 3T3-L1 cells through direct activation of caspase-3 [56]. Regardless of the molecular targets of capsinoids, the precise tissues by which they affect body weight present an important therapeutic potential. Multiple studies indicate an important role of vagal afferent neurons innervating the gastrointestinal tract in inducing autonomous nervous activity [57,58]. Capsiate, a digestion-vulnerable capsaicin analog, induces a BAT sympathetic nerve activity response when delivered via an intragastric route and is inhibited by vagotomy of the gastrointestinal vagal nerve [58]. Taken together, these findings suggest that TRPV1 and its ligands are important players in the onset of obesity and adipose gain, and a better understanding of the physiological role of TRPV1 in visceral afferents is necessary.

A fundamental output of activating TRPV1 in spinal nerves from the DRG is the secretion of multiple neuropeptides from the terminals of primary sensory neurons including the tachynins, CGRP, neurokinin A (NKA), and SP involved in neurogenic inflammation [59]. Among these substances, CGRP is the main neurotransmitter in the nociceptive C sensory nerves and a potent vasodilator and hypotensive agent implicated in chronic pain and migraines [60]. CGRP

mediates distinct pro- and anti-inflammatory immune activities, which implicate this peptide in neuroimmunological communication [61,62]. Because TRPV1 is a polymodal receptor activated by many reagents in the inflammatory milieu [63], it is plausible that the low-grade inflammation observed during obesity and diabetes sustains TRPV1 activation and exacerbates CGRP release, thus negatively impacting metabolic health. In accordance with this hypothesis, mutation of α-CGRP protects against diet-induced obesity by increasing energy expenditure, as observed in TRPV1 mutant mice [64]. Much evidence in the literature supports a role for CGRP in antagonizing insulin release from β cells *in vitro* and *in vivo* [51,65–73]. There is a strong distribution of spinal afferents in the pancreas, mostly originating from the DRG and positive for TRPV1 and CGRP [74]. The broad distribution of CGRP fibers and their association with immune cells including dendritic cells, mast cells, and T cells places CGRP as a key mediator of neuroimmune communication with the sensory fibers participating in the mediation of sensory signals as well as a controller of immune function [61]. It is probable that a better understanding of the neural–immune interaction will uncover key mechanisms for the treatment of metabolic diseases.

Sensory Neurons in Control of Longevity

Invertebrate models have provided ample proof that environmental perception can impact physiological functions ranging from development to aging. *C. elegans* nematodes possess a remarkable form of developmental plasticity, as they integrate sensory information received by ciliated sensory neurons, including food availability, temperature, and worm density, to arrest their development and form long-lived and stress-resistant dauer larvae [75,76]. Similarly, worms assess the same cues to decide whether to recover and resume normal development.

Laser ablation of chemosensory neurons in the worm extends lifespan [28,29] and mutations that impair chemosensory signal transduction increase longevity in both worms and flies [28,77]. In addition, flies lacking the odorant receptor *Or83b* are long lived, and present a normal metabolic rate but increased triglyceride storage, which conveys resistance to both starvation and hyperoxia [77].

Thus, the ability to affect aging by manipulating chemosensory neurons in invertebrate models provides evidence for evolutionary conservation and suggests that homologous and analogous circuits in mammalian models may exist. As mentioned above (see section on visceral sensing), evidence of the conserved function of chemosensory neurons in the regulation of longevity has been provided through the study of TRPV1 [51]. Impairment of TRPV1 sensory receptors is sufficient to extend mouse lifespan and improve metabolic health, acting remotely on pancreatic β cells to improve β cell mass and insulin secretion [51]. DRG sensory neurons form a dense meshwork innervating the pancreas and release CGRP neuropeptides, levels of which rise with age and antagonize insulin secretion [55]. Pharmacologic inhibition of CGRP receptors restores metabolic health in old mice, as observed on genetic deletion of TRPV1 [51]. The causal role of CGRP in regulating longevity remains unknown; however, considerable lifespan extension is observed in a rodent naturally lacking CGRP: the naked mole rat, which lives about 30 years and is the longest-lived rodent. By comparison, mice, which are of a similar size, have a maximum lifespan of 4 years. In addition to their longevity, naked mole rats are fully resistant to cancer, which is reduced in TRPV1 knockout mice [51]. However, whether CGRP plays a role in the extreme longevity of the naked mole rat is unknown and other mediators of this exceptional lifespan have been suggested. For example, naked mole rat fibroblasts secrete extremely high-molecular-mass hyaluronan that is over five times larger than the human or mouse homolog and prevents tumorigenesis in this species [78,79].

However, loss of sensory perception does not always correlate positively with increased lifespan. Olfactory dysfunction is a strong predictor of 5-year mortality in humans [80]. Loss of smell

is an independent risk factor for death – stronger than several common causes of mortality such as heart failure, lung disease, and cancer – pinpointing that this sense plays a role in human longevity [80]. Rather than its decline being causal for aging and death, it is highly plausible that olfaction represents the 'miner's canary' of human health and is a fundamental harbinger of cognitive decline, aging, and disease. Loss of olfactory sensitivity occurs in presymptomatic Alzheimer's disease [81], Parkinson's disease [82], and cognitive loss during aging [83]. The unique feature of the olfactory system relies on the constant turnover of olfactory sensory neurons in the oral mucosa and the olfactory bulb and therefore on regeneration from the stem cell pool located in the basal layer of the MOE and the brain subventricular zone [84]. Thus, olfactory loss may serve more generally as an indicator of deterioration in age-related regenerative capacity or as a marker of physiologic repair function [80].

Concluding Remarks

We have reviewed the recent literature implicating sensory neurons in the control of metabolism and longevity. Most of the available information concerning the role of olfactory and gustatory sensory neurons in energy balance is related to their ability to modulate feeding behaviors. Emerging research has highlighted the recruitment of endocrine signaling in modulating olfactory and gustatory signaling, fine-tuning these systems depending on the nutritional status of the animal. Future work focusing on the interplay between these systems will be fundamental to update the current view of the exclusive regulation of hypothalamic feeding circuits by hormonal signals such as ghrelin, leptin, insulin, and GLP-1.

At present, the picture that emerges from the study of sensory neurons in the regulation of aging is still incomplete. Although much evidence has been gathered from invertebrate systems, the exploration of the role of these neurons in mammalian aging remains largely unknown. It will be fascinating to explore the role of olfactory and gustatory neurons in the regulation of mammalian aging. The current knowledge implicating mammalian sensory neurons in longevity comes from the study of TRPV1. The physiological function of TRPV1 sensory nerves beyond the control of insulin secretion with age remains poorly understood and more work is required to determine how the broad distribution of these neurons impacts physiological functions in other tissues. In particular, the ambiguous role of the neurogenic signal secreted by these neurons, CGRP, in the regulation of inflammation and immune function remains to be determined. What role does CGRP play in the dissemination of the low-grade inflammatory response associated with aging? By gaining better knowledge of the role of sensory neurons in energy balance and aging, and manipulating these sensory neuroendocrine processes to extend health span and lifespan, it might become possible to translate these findings to treat metabolic and age-associated diseases.

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Disclaimer Statement

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References

1. Cowley, M.A. *et al.* (2001) Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus. *Nature* 411, 480–484
2. Hahn, T.M. *et al.* (1998) Coexpression of Agrp and NPY in fasting-activated hypothalamic neurons. *Nat. Neurosci.* 1, 271–272
3. Huszar, D. *et al.* (1997) Targeted disruption of the melanocortin-4 receptor results in obesity in mice. *Cell* 88, 131–141
4. Fan, W. *et al.* (1997) Role of melanocortinergic neurons in feeding and the agouti obesity syndrome. *Nature* 385, 165–168
5. Gropp, E. *et al.* (2005) Agouti-related peptide-expressing neurons are mandatory for feeding. *Nat. Neurosci.* 8, 1289–1291
6. Luquet, S. *et al.* (2005) NPY/AgRP neurons are essential for feeding in adult mice but can be ablated in neonates. *Science* 310, 683–685

Outstanding Questions

What are the neuronal circuits linking olfactory input to appetite and satiety neuronal responses? The hypothalamus receives indirect inputs from OSNs through signals incoming from the MOB and transmitted to the centers of the olfactory cortex. Some direct connections between discrete subpopulations of OSNs and several hypothalamic nuclei, such as the PVN, the supraoptic nucleus (SO), and luteinizing hormone-releasing hormone (LHRH)-secreting neurons have been observed [85,86], suggesting the existence of an active circuitry initiated from OSNs to the hypothalamus to influence metabolic homeostasis.

Do gut taste-like enteroendocrine L cells signal food and bacterial gut content to the hypothalamus? These cells secrete GLP-1 in a glucose-dependent manner and are ideally situated to sense luminal contents and transmit signals in influence nutrient uptake and satiety signals in the brain. The presence of an α-MSH mimetic whose levels correlate with the presence of food in the gut and that is capable of stimulating enteroendocrine melanocortin receptors suggests a prominent role of these cells in controlling energy balance.

What are the endogenous agents that modulate TRPV1 receptors on afferent sensory nerves from the DRG during aging and obesity? As TRPV1 is a multimodal receptor targeted by many components of the inflammatory soup, it will be critical to determine whether a specific stimulus exacerbates TRPV1 activity and sustains CGRP release to cause metabolic decline.

CGRP mediates distinct pro-and anti-inflammatory immune activities, implicating this peptide in neuroimmunological communication. What is the role of CGRP in metabolic diseases and aging with regard to modulating the immune function of dendritic cells, mast cells, and T cells.

To what degree do the promising animal data on obesity and aging apply to humans? The quest for conservation of the neuroendocrine role of sensory neurons from invertebrate to mammalian models is at an early stage and studies investigating these processes in humans are needed. Sensory neurons might hold promise for a new therapeutic era in diabetes and age-associated diseases.

7. Carter, M.E. *et al.* (2013) Genetic identification of a neural circuit that suppresses appetite. *Nature* 503, 111–114
8. Becskei, C. *et al.* (2007) Lesion of the lateral parabrachial nucleus attenuates the anorectic effect of peripheral amylin and CCK. *Brain Res.* 1162, 76–84
9. King, B.M. *et al.* (1994) Effect on food intake and body weight of lesions in and adjacent to the posterodorsal amygdala in rats. *Physiol. Behav.* 55, 963–966
10. Yamamoto, T. (2007) Brain regions responsible for the expression of conditioned taste aversion in rats. *Chem. Senses* 32, 105–109
11. Jennings, J.H. *et al.* (2013) The inhibitory circuit architecture of the lateral hypothalamus orchestrates feeding. *Science* 341, 1517–1521
12. Chen, Y. *et al.* (2015) Sensory detection of food rapidly modulates arcuate feeding circuits. *Cell* 160, 829–841
13. Mainland, J.D. *et al.* (2014) From molecule to mind: an integrative perspective on odor intensity. *Trends Neurosci.* 37, 443–454
14. Albrecht, J. *et al.* (2009) Olfactory detection thresholds and pleasantness of a food-related and a non-food odour in hunger and satiety. *Rhinology* 47, 160–165
15. Cameron, J.D. *et al.* (2012) Fasting for 24 h improves nasal chemosensory performance and food palatability in a related manner. *Appetite* 58, 978–981
16. Tong, J. *et al.* (2011) Ghrelin enhances olfactory sensitivity and exploratory sniffing in rodents and humans. *J. Neurosci.* 31, 5841–5846
17. Soria-Gómez, E. *et al.* (2014) Cannabinoid type-1 receptors in the paraventricular nucleus of the hypothalamus inhibit stimulated food intake. *Neuroscience* 263, 46–53
18. Savigner, A. *et al.* (2009) Modulation of spontaneous and odorant-evoked activity of rat olfactory sensory neurons by two anorectic peptides, insulin and leptin. *J. Neurophysiol.* 101, 2898–2906
19. Elmquist, J.K. *et al.* (1998) Distributions of leptin receptor mRNA isoforms in the rat brain. *J. Comp. Neurol.* 395, 535–547
20. Shioda, S. *et al.* (1998) Immunohistochemical localization of leptin receptor in the rat brain. *Neurosci. Lett.* 243, 41–44
21. Getchell, T.V. *et al.* (2006) Leptin regulates olfactory-mediated behavior in *ob/ob* mice. *Physiol. Behav.* 87, 848–856
22. Hill, J.M. *et al.* (1986) Autoradiographic localization of insulin receptors in rat brain: prominence in olfactory and limbic areas. *Neuroscience* 17, 1127–1138
23. Baskin, D.G. *et al.* (1983) Regional concentrations of insulin in the rat brain. *Endocrinology* 112, 898–903
24. Banks, W.A. *et al.* (1999) Uptake and degradation of blood-borne insulin by the olfactory bulb. *Peptides* 20, 373–378
25. Perassi, N.I. *et al.* (1975) Removal of olfactory bulbs in rats of different ages: repercussion on some metabolic constants. *Arch. Int. Physiol. Biochim.* 83, 855–862
26. Xu, J. *et al.* (2003) The voltage-gated potassium channel Kv1.3 regulates energy homeostasis and body weight. *Hum. Mol. Genet.* 12, 551–559
27. Tucker, K. *et al.* (2012) Diet-induced obesity resistance of Kv1.3$^{-/-}$ mice is olfactory bulb dependent. *J. Neuroendocrinol.* 24, 1087–1095
28. Alcedo, J. and Kenyon, C. (2004) Regulation of *C. elegans* longevity by specific gustatory and olfactory neurons. *Neuron* 41, 45–55
29. Apfeld, J. and Kenyon, C. (1999) Regulation of lifespan by sensory perception in *Caenorhabditis elegans*. *Nature* 402, 804–809
30. Leinwand, S.G. *et al.* (2015) Circuit mechanisms encoding odors and driving aging-associated behavioral declines in *Caenorhabditis elegans*. *Elife* 4, e10181
31. Primeaux, S.D. *et al.* (2007) Olfactory bulbectomy increases food intake and hypothalamic neuropeptide Y in obesity-prone but not obesity-resistant rats. *Behav. Brain Res.* 180, 190–196
32. Oral, E. *et al.* (2013) How olfaction disorders can cause depression? The role of habenular degeneration. *Neuroscience* 240, 63–69
33. Nelson, G. *et al.* (2001) Mammalian sweet taste receptors. *Cell* 106, 381–390
34. Kawai, K. *et al.* (2000) Leptin as a modulator of sweet taste sensitivities in mice. *Proc. Natl. Acad. Sci. U.S.A.* 97, 11044–11049
35. Yoshida, R. *et al.* (2015) Leptin suppresses mouse taste cell responses to sweet compounds. *Diabetes* 64, 3751–3762
36. Yoshida, R. *et al.* (2010) Endocannabinoids selectively enhance sweet taste. *Proc. Natl. Acad. Sci. U.S.A.* 107, 935–939
37. Ren, X. *et al.* (2010) Nutrient selection in the absence of taste receptor signaling. *J. Neurosci.* 30, 8012–8023
38. Zukerman, S. *et al.* (2013) Post-oral appetite stimulation by sugars and nonmetabolizable sugar analogs. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 305, R840–R853
39. Delaere, F. *et al.* (2013) Portal glucose influences the sensory, cortical and reward systems in rats. *Eur. J. Neurosci.* 38, 3476–3486
40. Otsubo, H. *et al.* (2011) Induction of Fos expression in the rat forebrain after intragastric administration of monosodium L-glutamate, glucose and NaCl. *Neuroscience* 196, 97–103
41. von Holstein-Rathlou, S. *et al.* (2016) FGF21 mediates endocrine control of simple sugar intake and sweet taste preference by the liver. *Cell Metab.* 23, 335–343
42. Potthoff, M.J. *et al.* (2012) Endocrine fibroblast growth factors 15/19 and 21: from feast to famine. *Genes Dev.* 26, 312–324
43. Janssen, S. and Depoortere, I. (2013) Nutrient sensing in the gut: new roads to therapeutics? *Trends Endocrinol. Metab.* 24, 92–100
44. Jang, H-J. *et al.* (2007) Gut-expressed gustducin and taste receptors regulate secretion of glucagon-like peptide-1. *Proc. Natl. Acad. Sci. U.S.A.* 104, 15069–15074
45. Breton, J. *et al.* (2015) Gut commensal E. coli proteins activate host satiety pathways following nutrient-induced bacterial growth. *Cell Metab.* 23, 324–334
46. Panaro, B.L. *et al.* (2014) The melanocortin-4 receptor is expressed in enteroendocrine L cells and regulates the release of peptide YY and glucagon-like peptide 1 *in vivo*. *Cell Metab.* 20, 1018–1029
47. Christianson, J.A. and Davis, B.M. (2010) The role of visceral afferents in disease. In *Translational Pain Research: From Mouse to Man* (Kruger, L. and Light, A.R., eds), pp. 51–76, CRC Press
48. Caterina, M.J. *et al.* (1997) The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature* 389, 816–824
49. Ahern, G.P. (2013) Transient receptor potential channels and energy homeostasis. *Trends Endocrinol. Metab.* 24, 554–560
50. Motter, A.L. and Ahern, G.P. (2008) TRPV1-null mice are protected from diet-induced obesity. *FEBS Lett.* 582, 2257–2262
51. Riera, C.E. *et al.* (2014) TRPV1 pain receptors regulate longevity and metabolism by neuropeptide signaling. *Cell* 157, 1023–1036
52. Snitker, S. *et al.* (2009) Effects of novel capsinoid treatment on fatness and energy metabolism in humans: possible pharmacogenetic implications. *Am. J. Clin. Nutr.* 89, 45–50
53. Westerterp-Plantenga, M.S. *et al.* (2005) Sensory and gastrointestinal satiety effects of capsaicin on food intake. *Int. J. Obes. (Lond.)* 29, 682–688
54. Kawada, T. *et al.* (1988) Some pungent principles of spices cause the adrenal medulla to secrete catecholamine in anesthetized rats. *Proc. Soc. Exp. Biol. Med.* 188, 229–233
55. Melnyk, A. and Himms-Hagen, J. (1995) Resistance to aging-associated obesity in capsaicin-desensitized rats one year after treatment. *Obes. Res.* 3, 337–344
56. Jung, M-Y. *et al.* (2001) Capsaicin-induced apoptosis in SK-Hep-1 hepatocarcinoma cells involves Bcl-2 downregulation and caspase-3 activation. *Cancer Lett.* 165, 139–145
57. Kawabata, F. *et al.* (2006) Effects of CH-19 sweet, a non-pungent cultivar of red pepper, in decreasing the body weight and suppressing body fat accumulation by sympathetic nerve activation in humans. *Biosci. Biotechnol. Biochem.* 70, 2824–2835
58. Ono, K. *et al.* (2011) Intragastric administration of capsiate, a transient receptor potential channel agonist, triggers thermogenic sympathetic responses. *J. Appl. Physiol. (1985)* 110, 789–798
59. Benemei, S. *et al.* (2009) CGRP receptors in the control of pain and inflammation. *Curr. Opin. Pharmacol.* 9, 9–14

60. Springer, J. *et al.* (2003) Calcitonin gene-related peptide as inflammatory mediator. *Pulm. Pharmacol. Ther.* 16, 121–130
61. Assas, B.M. *et al.* (2014) Calcitonin gene-related peptide is a key neurotransmitter in the neuro-immune axis. *Front. Neurosci.* 8, 23
62. Harzenetter, M.D. *et al.* (2007) Negative regulation of TLR responses by the neuropeptide CGRP is mediated by the transcriptional repressor ICER. *J. Immunol.* 179, 607–615
63. Suri, A. and Szallasi, A. (2008) The emerging role of TRPV1 in diabetes and obesity. *Trends Pharmacol. Sci.* 29, 29–36
64. Walker, C.S. *et al.* (2010) Mice lacking the neuropeptide alpha-calcitonin gene-related peptide are protected against diet-induced obesity. *Endocrinology* 151, 4257–4269
65. Ahrén, B. *et al.* (1987) Effects of calcitonin gene-related peptide (CGRP) on islet hormone secretion in the pig. *Diabetologia* 30, 354–359
66. Akiba, Y. *et al.* (2004) Transient receptor potential vanilloid subfamily 1 expressed in pancreatic islet β cells modulates insulin secretion in rats. *Biochem. Biophys. Res. Commun.* 321, 219–225
67. Asahina, A. *et al.* (1995) Specific induction of cAMP in Langerhans cells by calcitonin gene-related peptide: relevance to functional effects. *Proc. Natl. Acad. Sci. U.S.A.* 92, 8323–8327
68. Gram, D.X. (2005) Plasma calcitonin gene-related peptide is increased prior to obesity, and sensory nerve desensitization by capsaicin improves oral glucose tolerance in obese Zucker rats. *Eur. J. Endocrinol.* 153, 963–969
69. Gram, D.X. *et al.* (2007) Capsaicin-sensitive sensory fibers in the islets of Langerhans contribute to defective insulin secretion in Zucker diabetic rat, an animal model for some aspects of human type 2 diabetes. *Eur. J. Neurosci.* 25, 213–223
70. Kogire, M. *et al.* (1991) Inhibitory action of islet amyloid polypeptide and calcitonin gene-related peptide on release of insulin from the isolated perfused rat pancreas. *Pancreas* 6, 459–463
71. Lewis, C.E. *et al.* (1988) Calcitonin gene-related peptide and somatostatin inhibit insulin release from individual rat B cells. *Mol. Cell. Endocrinol.* 57, 41–49
72. Pettersson, M. *et al.* (1986) Calcitonin gene-related peptide: occurrence in pancreatic islets in the mouse and the rat and inhibition of insulin secretion in the mouse. *Endocrinology* 119, 865–869
73. Tanaka, H. *et al.* (2011) Enhanced insulin secretion and sensitization in diabetic mice on chronic treatment with a transient receptor potential vanilloid 1 antagonist. *Life Sci.* 88, 559–563
74. Fasanella, K.E. *et al.* (2008) Distribution and neurochemical identification of pancreatic afferents in the mouse. *J. Comp. Neurol.* 509, 42–52
75. Bargmann, C.I. (2006) Chemosensation in *C. elegans*. *www.ncbi.nlm.nih.gov/books/NBK19746/*
76. Golden, J.W. and Riddle, D.L. (1982) A pheromone influences larval development in the nematode *Caenorhabditis elegans*. *Science* 218, 578–580
77. Libert, S. *et al.* (2007) Regulation of *Drosophila* life span by olfaction and food-derived odors. *Science* 315, 1133–1137
78. Seluanov, A. *et al.* (2009) Hypersensitivity to contact inhibition provides a clue to cancer resistance of naked mole-rat. *Proc. Natl. Acad. Sci. U.S.A.* 106, 19352–19357
79. Tian, X. *et al.* (2013) High-molecular-mass hyaluronan mediates the cancer resistance of the naked mole rat. *Nature* 499, 346–349
80. Pinto, J.M. *et al.* (2014) Olfactory dysfunction predicts 5-year mortality in older adults. *PLoS ONE* 9, e107541
81. Wilson, R.S. *et al.* (2009) Olfactory impairment in presymptomatic Alzheimer's disease. *Ann. N. Y. Acad. Sci.* 1170, 730–735
82. Ross, G.W. *et al.* (2008) Association of olfactory dysfunction with risk for future Parkinson's disease. *Ann. Neurol.* 63, 167–173
83. Graves, A.B. *et al.* (1999) Impaired olfaction as a marker for cognitive decline: interaction with apolipoprotein E ε4 status. *Neurology* 53, 1480
84. Pignatelli, A. and Belluzzi, O. (2010) Neurogenesis in the adult olfactory bulb. In *The Neurobiology of Olfaction* (Menini, A., ed.), pp. 267–304, CRC Press/Taylor & Francis
85. Bader, A. *et al.* (2012) Connectivity from OR37 expressing olfactory sensory neurons to distinct cell types in the hypothalamus. *Front. Neural Circuits* 6, 84
86. Yoon, H. *et al.* (2005) Olfactory inputs to hypothalamic neurons controlling reproduction and fertility. *Cell* 123, 669–682